Update on blood based biomarkers for Alzheimer's Disease

David M. Holtzman, MD
Professor and Chair of Neurology
Washington University in St. Louis

Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Washington University in St. Louis

hopecenter for neurological disorders

Disclosures

Co-founder, C2N Diagnostics LLC.

Scientific advisory boards/consulting: Genentech, C2N Diagnostics, Denali, Merck, Cajal Neurosciences, Annexon

David Holtzman is an inventor on a patents licensed by Washington University to 1) C2N Diagnostics on the therapeutic use of anti-tau antibodies. This anti-tau antibody program is licensed to Abbvie and 2) Eli Lilly on the therapeutic use of an anti-amyloid-β antibody; 3) materials and methods related to assessing Aβ and tau in plasma blood tests.

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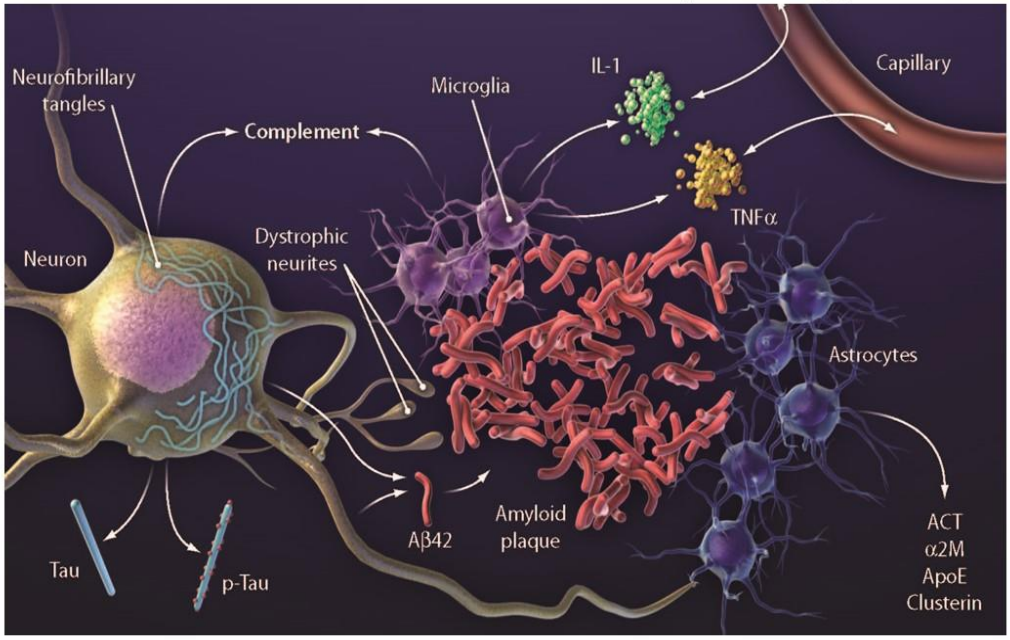
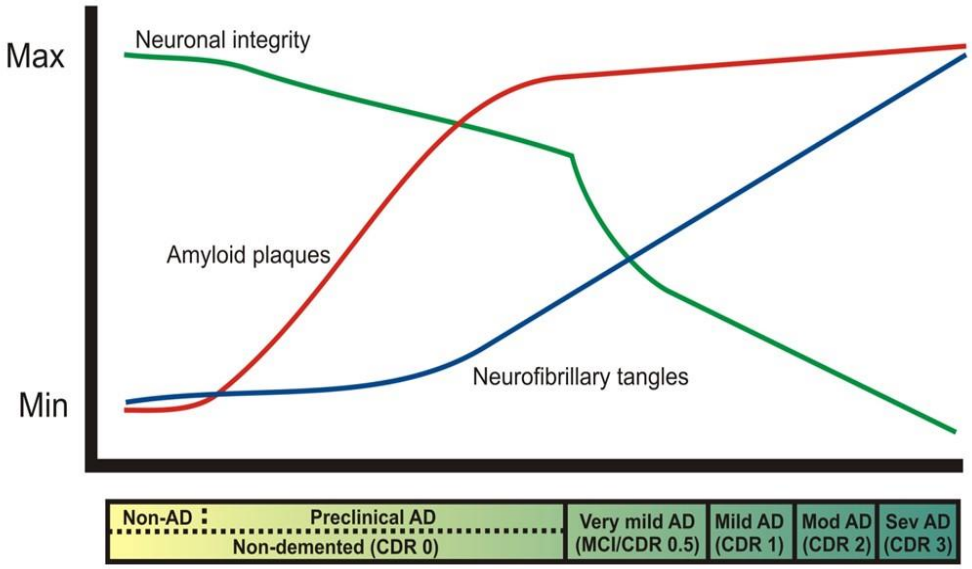
Model of Alzheimer's brain pathology

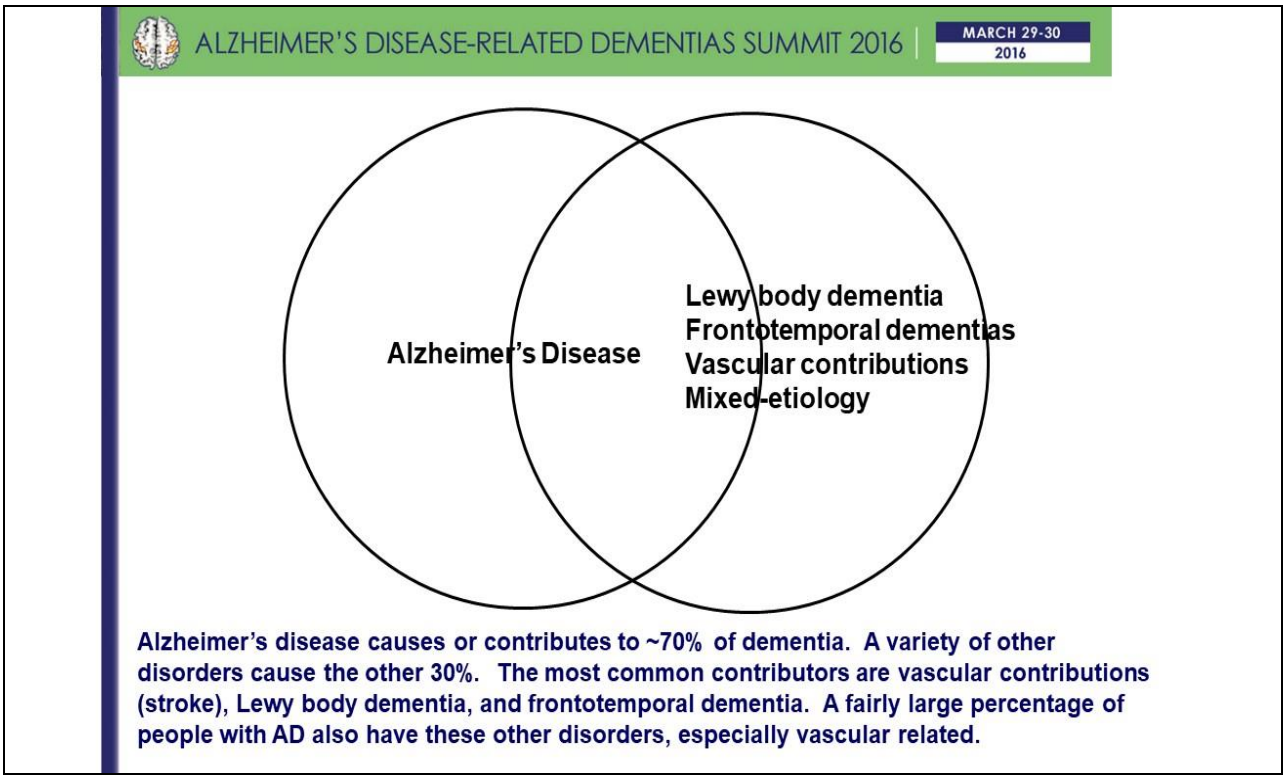


Holtzman DM, Morris JC, Goate AM (2011) Science Translational Medicine Vol 3, Issue 77

AD pathological changes in relation to clinical manifestations



Perrin, Fagan, and Holtzman, Nature. 2009, 461:916-922



What is a biomarker?

World Health Organization:

Almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical, or biological. The measured response may be functional and physiological, biochemical at the cellular level, or a molecular interaction.

Examples in medicine of biomarkers include: pulse, blood pressure, LDL and HDL cholesterol

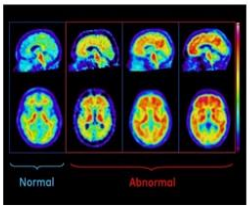
In the case of Alzheimer's disease (AD), the biomarkers to be discussed today are those that objectively mark aspects of AD pathology in the brain: amyloid plaques, neuronal response to amyloid, tau tangles, and neurodegeneration (brain injury/cell death).

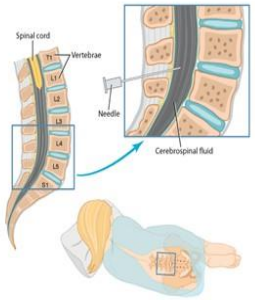
How are AD biomarkers used?

- Research- to understand underlying causes of AD pathophysiology
- Clinical trials
  - Treatment trials- To confirm that AD is the likely cause of cognitive impairment
  - Prevention trials- To identify cognitively normal participants with AD brain pathology
  - Target engagement- To confirm that drugs are affecting AD-related targets
- Clinic
  - Currently, to evaluate for AD brain pathology in patients where the clinician suspects AD as the cause of cognitive symptoms but is uncertain
  - In the future, when we have disease-modifying therapies (e.g. pills, antibody injections, other interventions), a test confirming underlying AD pathology will be likely be required to start treatment

Limitations to imaging- and CSF-based AD tests

- **Amyloid PET**:
  - Expensive (~$5,000/scan) and not covered by insurance
  - Limited availability (only major medical centers)
  - Small amount of radiation
- **CSF biomarkers**:
  - Lumbar puncture may be perceived as invasive
  - Small but real risks of headache or back soreness
  - Somewhat expensive (~$750 or more just for Aβ42, Aβ40, tau, ptau181, depending on company); requires time from physician/staff that may not be adequately compensated
  - Not convenient

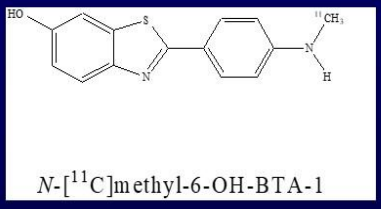




Advantages of a blood test

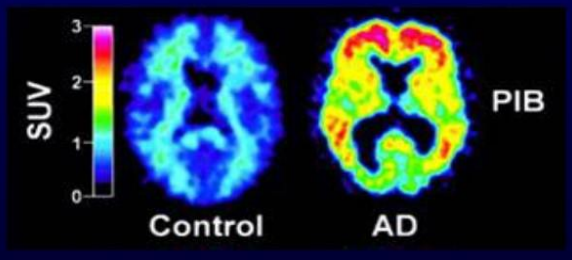
- **Practical advantages**
  - Individuals are comfortable having blood drawn
  - Blood can be drawn almost anywhere and samples can be shipped to a lab for testing
  - Lower costs may be possible (e.g. <$1,300)
- **Scientific advantages**
  - Multiple proteins can be measured with a single blood sample
  - Results are a number, rather than a more subjective "read," facilitating interpretation of results
  - Studies could measure AD biomarkers without burden of imaging/lumbar puncture
- **Potential impact on clinical trials and the clinic**
  - Participants in clinical trials could be screened/recruited more rapidly and cost-effectively, speeding development of effective treatments
  - Currently, <~5% of dementia patients are evaluated with AD biomarkers—if an accurate blood test is developed, this could increase to ~80%
  - More widespread use of blood-based biomarkers could potentially lead to earlier and more accurate diagnosis of AD dementia

Cerebral binding of the amyloid-binding molecule, [^{11}C]PIB, is a biomarker of amyloid plaques, detected by a PET scan



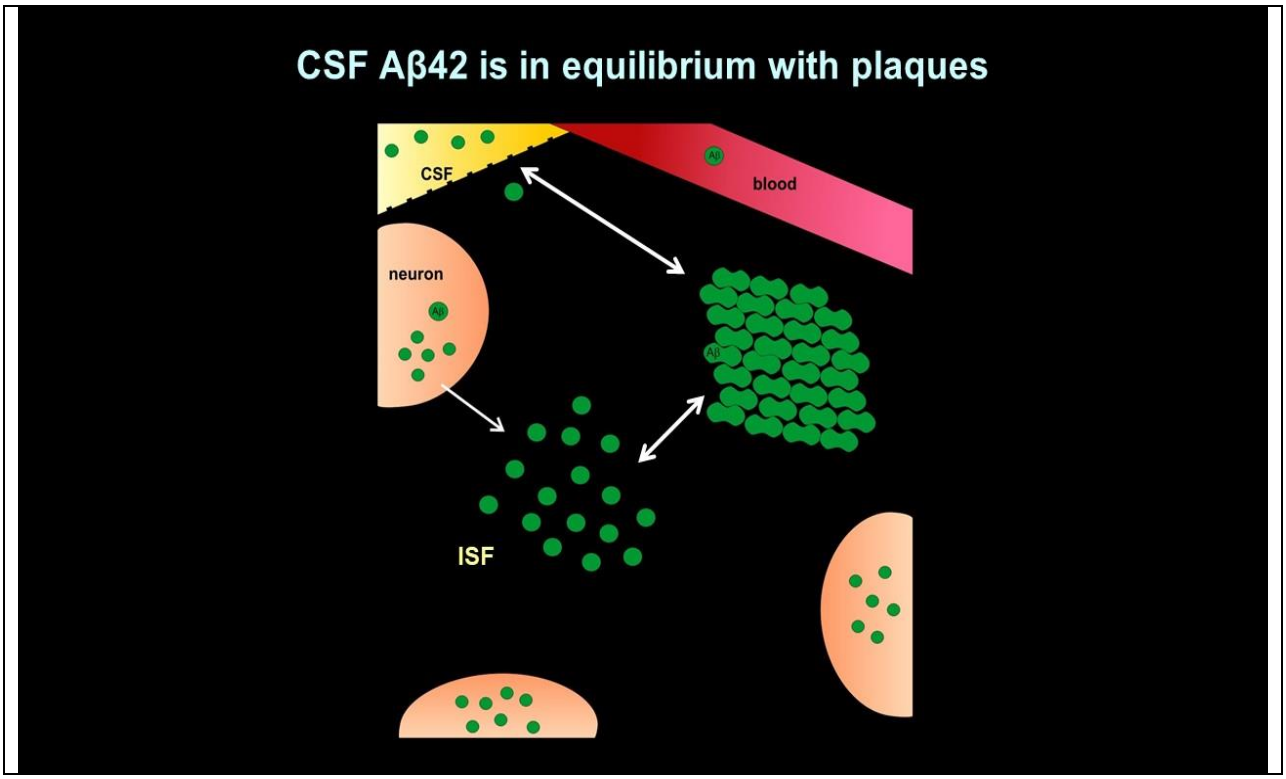
N-[^{11}C]methyl-6-OH-BTA-1

[^{11}C]PIB: benzothiazole analog,
Pittsburgh Compound B, tagged for PET

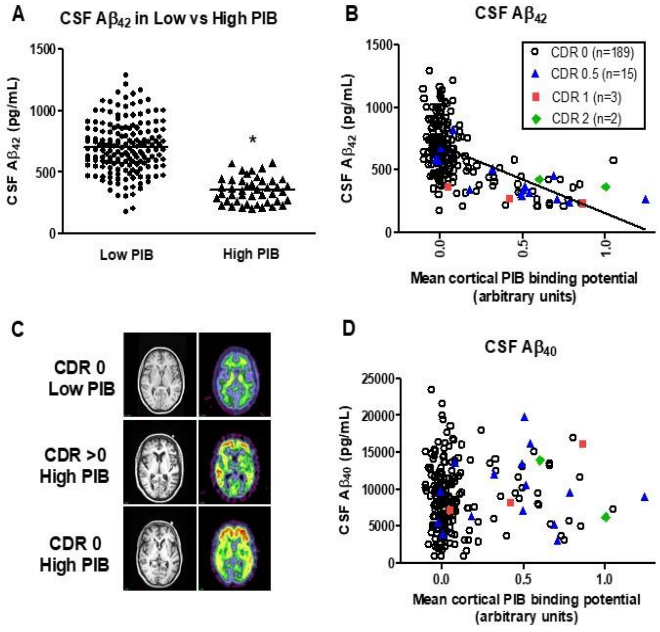


(adapted from Klunk et al., 2004, *Ann. Neurol.55:306-19)*

CSF Aβ42 is in equilibrium with plaques



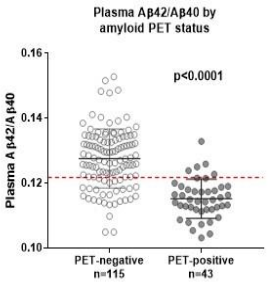
Normal and demented subjects with amyloid in the brain have a low CSF Aβ42 (N=209)



Fagan AM et al. 2009 EMBO Mol. Med, 1:371-380

Plasma Aβ42/Aβ40 = amyloid PET?

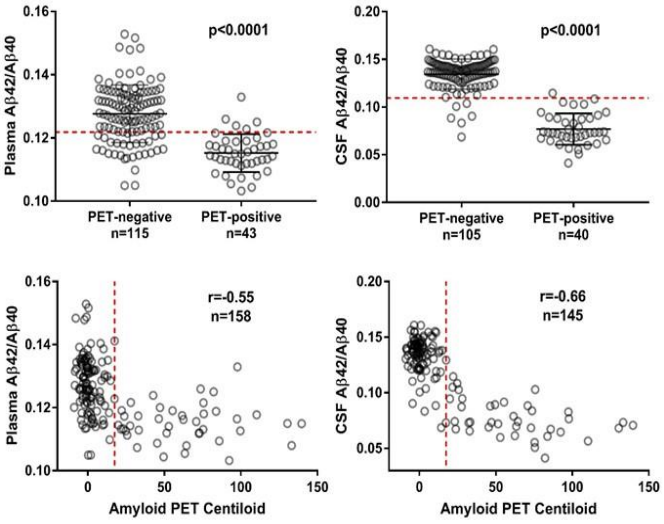
- Normalizing Aβ42 to Aβ40 likely accounts for some pre-analytical variation and individual differences in Aβ production and diurnal variation; Aβ42/Aβ40 is a measure of Aβ42 sequestration into plaques just like in CSF.
- The difference between abnormal and normal is small (~10%), so a precise assay is required
- Multiple groups have reported that high precision assays for Aβ42/Aβ40 using mass spec are highly concordant with amyloid PET[1-4], especially after consideration of *APOE* ε4 genotype[3,4]
- "False positive" plasma Aβ42/Aβ40 results predict conversion to amyloid PET positive; plasma may be positive before amyloid PET[4]



[1]Ovod *A&D* 2017; [2]Nakamura *Nature* 2018; [3]Verberk *Ann Neurol* 2018

[4]Schindler S… Bateman R. *Neurology* 2019

Plasma and CSF Aβ42/40 identifies is useful in identifying those who are have amyloid in brain as see via PET scan



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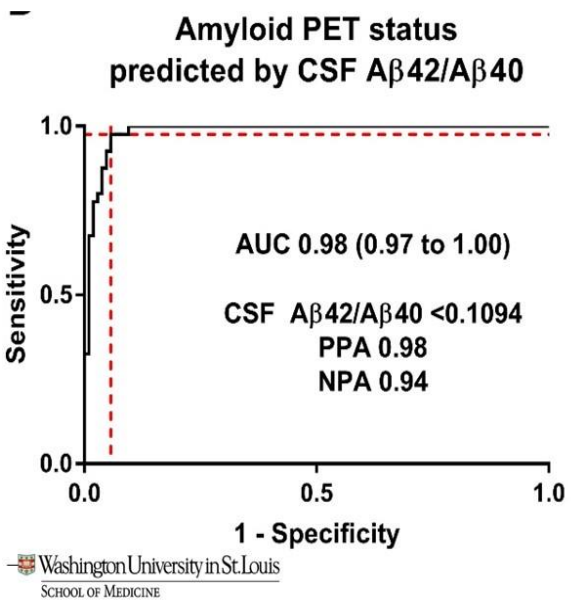
Plasma Aβ42/40 highly specific for gold-standard measures of amyloid PET and can perform as well as CSF or PET compared to pathologic confirmation (AUC ~0.9) with age and ApoE status



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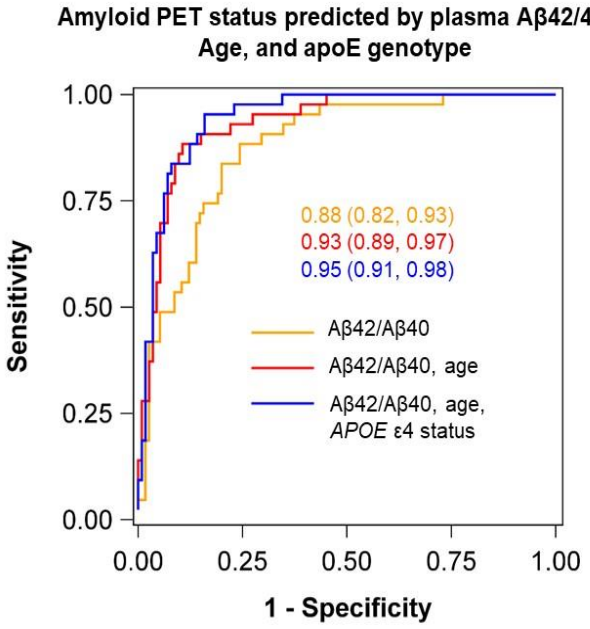
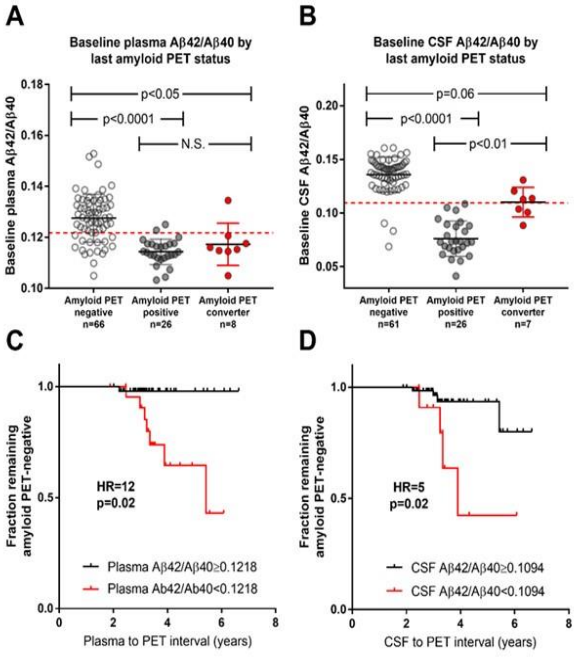


Baseline plasma and CSF Aβ42/Aβ40 predict amyloid PET status conversion.

Individuals who were amyloid PET-negative at baseline and converted to amyloid PET-positive over the follow-up period had lower baseline plasma Aβ42/Aβ40 than individuals who remained amyloid PET-negative



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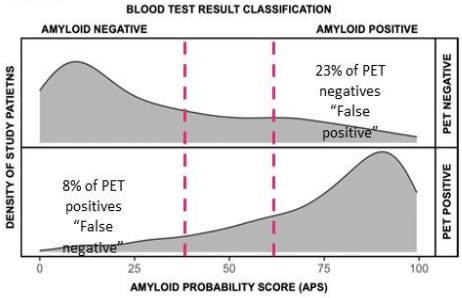
The first blood test for detection of amyloidosis in individuals with cognitive impairment is now available for clinical use

- PrecivityAD test from C2N Diagnostics (IPMS plasma Aβ42/Aβ40 + *APOE* genotype + age)

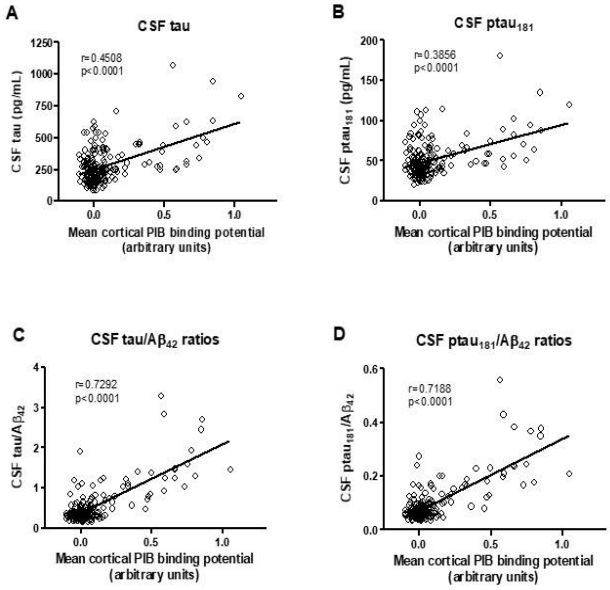


PrecivityAD™

https://precivityad.com

- More AD blood tests will likely follow soon (e.g. pTau181, pTau217, NfL)

Brain amyloid significantly correlates with CSF tau and tau/Aβ42 ratio in individuals who are cognitively normal (N=189)



Fagan AM et al. 2009 EMBO Mol. Med, 1:371-380

Time course of clinical and biomarker changes in dominantly inherited Alzheimer's disease in relation to expected parental age of dementia onset

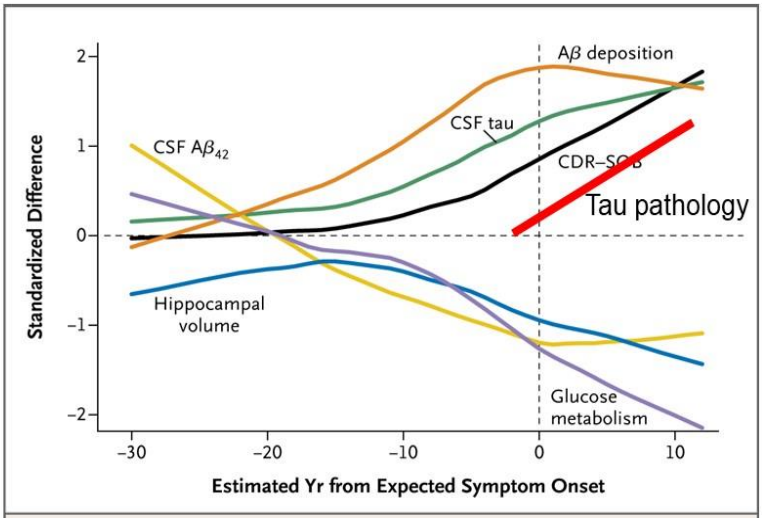
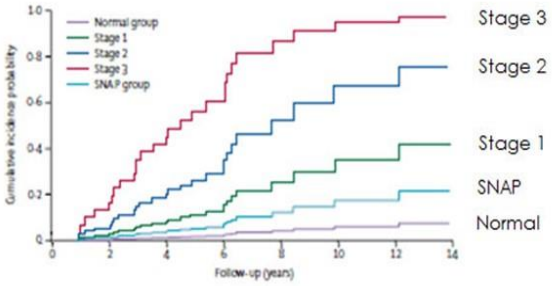


Figure 2. Comparison of Clinical, Cognitive, Structural, Metabolic, and Biochemical Changes as a Function of Estimated Years from Expected Symptom Onset.

Bateman R et al. from the DIAN Network 2012 NEJM 30;367(9):795-804

CSF tau and Aβ42 predict progression from cognitively normal to very mild dementia/MCI and MCI to AD

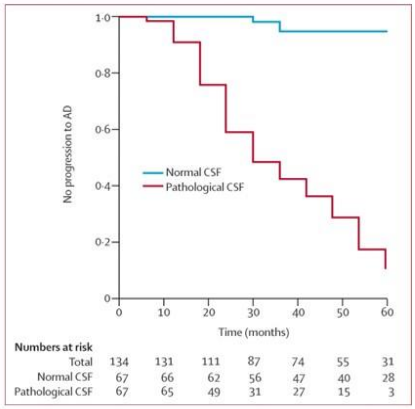
Normal to MCI/AD predicted by tau/Aβ42



Longitudinal follow up of N=297 research participants >65 years old, all cognitively normal at start. Elevated tau/Aβ42 in stage 2 and 3 participants

Vos SJ et al. 2013 Lancet Neurology 12:957-65
Craig-Schapiro R, et al. 2010 Biol. Psychiatry 2010 68:903-12
Tarawneh et al., 2011 Ann Neurol 70:274-85.
Fagan et al., 2007 Arch Neuro, 64:343-349
Li et al., 2007, Neurology, 69:631.

MCI to AD predicted by tau/Aβ42

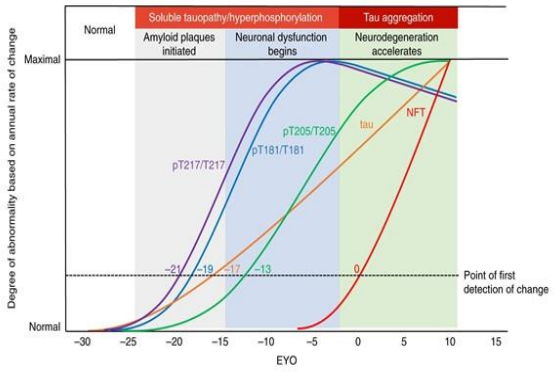


	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
Pathological CSF (T-tau and Aβ42)	30·0 (9·32–96·8)†	17·7 (5·33–58·9)†
Pathological CSF (P-tau$_{181}$ and Aβ42)	26·3 (8·16–84·5)†	16·8 (5·02–56·5)†

Hansson et al. 2006 Lancet Neurol. 5:228-234

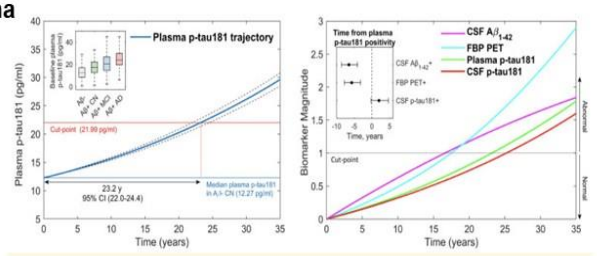
pTau isoforms may be helpful in staging AD

CSF

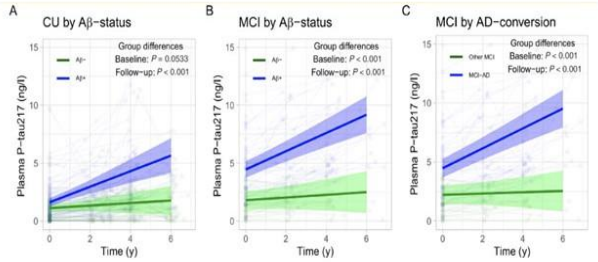


Barthelemy, et al. *Nature Med 2020*

Plasma



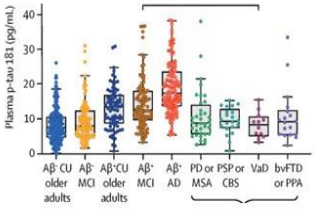
Moscoso et al. *Brain 2020*



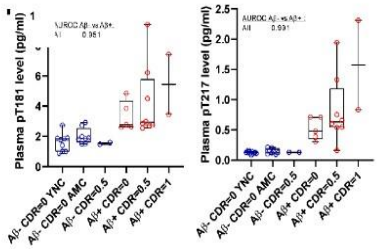
Mattsson-Carlgren et al. *Brain 2020*

Plasma pTau—better correspondence with symptoms

- Plasma pTau181[1-7] and pTau217[5,6,8]
  - Good concordance with both amyloid PET and tau PET but these ARE NOT markers of tau tangles – they are markers of amyloid induced effects on neurons
  - Can help differentiate Alzheimer disease from other neurological disorders
  - Predicts cognitive decline (pTau181)
  - Increases in later stages of the disease



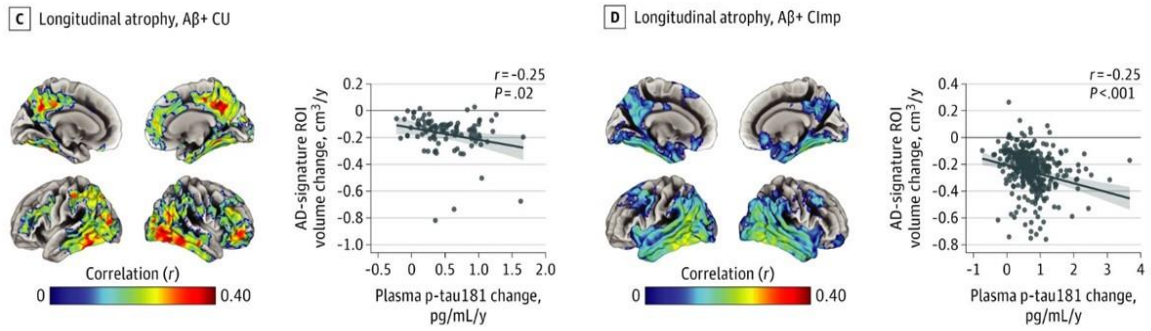
[4]Karikari *Lancet Neurol* 2020



[5]Barthelemy *J Exp Med 2020*

[1]Mielke A&D 2018; [2]Janelidze Nat Med 2020; [3]Thijssen *Nat Med* 2020, [6]Palmqvist *JAMA* 2020, [7]Moscoso *Brain 2020*, [8]Mattsson-Carlgren *Brain 2020*

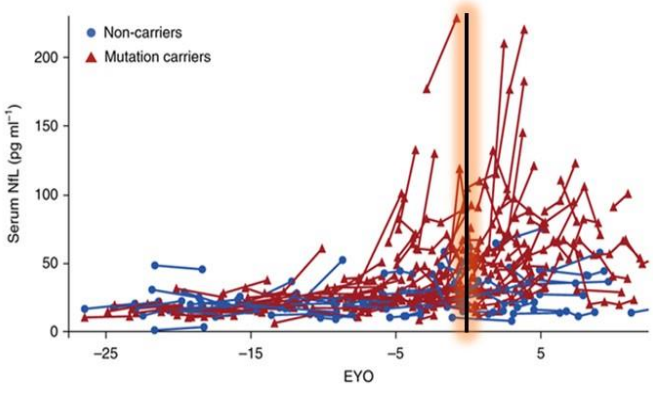
Plasma pTau – increases over time predicts brain atrophy but only in amyloid positive individuals



Moscoso A et al. JAMA Neurology 2021; doi:10.1001/jamaneurol.2020.4986

Plasma/serum NfL—non-specific neuroaxonal damage

- Plasma NfL is correlated with dementia and brain atrophy[1]
- Serum NfL increases fastest in individuals who are transitioning from cognitively normal to symptomatic[2]
- Faster increases in plasma NfL predict smaller brain volume and worse cognitive performance[3]

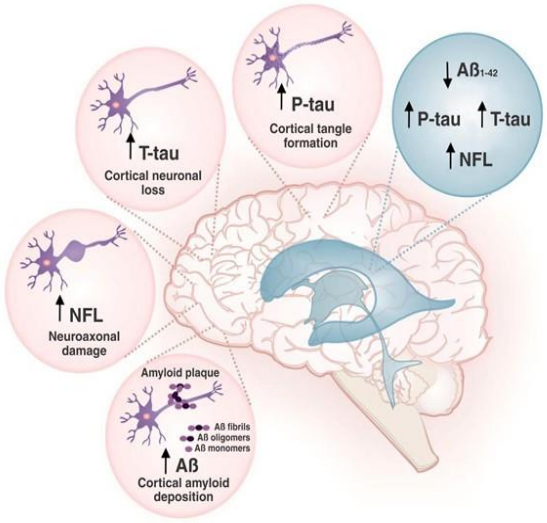


[2]Preische *Nat Med* 2019

[1]Mattsson *JAMA Neurol* 2017;
[3]Mattson *JAMA Neurol* 2019

Promising blood analytes

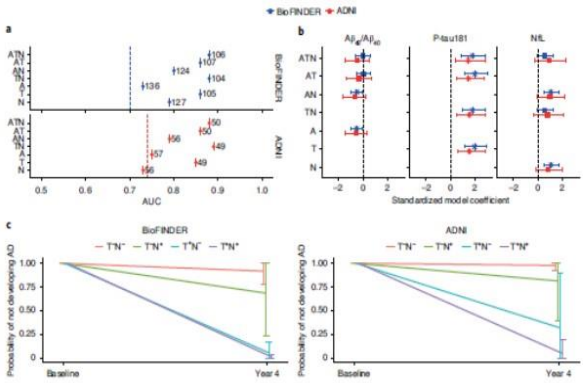
1. Aβ42/Aβ40
   - Becomes positive very early
   - Identified brain amyloidosis
2. Phosphorylated tau isoforms (including tau phosphorylated at T181, T217)
   - Increases during preclinical AD
   - Increases with increasing brain amyloidosis
3. Neurofilament light protein (NfL)
   - Not-specific for specific disease
   - But, tells one that there is ongoing neuronal damage



Radanovic *BrJPsy* 2019

Using plasma biomarkers in combination

- Future AD blood tests are likely to use a combination of biomarkers, rather than a single analyte, to predict risk for AD dementia
- Models including individual factors (age, sex, *APOE* genotype, race, etc., rather than a single cut-off value for positive/negative, are likely to be more accurate)



Cullen *Nature Aging* 2020

Overall conclusions

- Blood-based biomarkers provide similar information as amyloid PET and CSF biomarkers, but because of practical advantages, may enable broader use of AD biomarker testing
- When measured with a precise assay, plasma Aβ42/Aβ40 is highly concordant with amyloid PET status, especially after consideration of *APOE* ε4 status
- Plasma pTau isoforms are highly concordant with both amyloid PET status and symptomatic status and could potentially allow for staging of AD
- Widespread use of blood-based biomarkers in clinical diagnosis should lead to earlier and more accurate diagnosis of cognitive impairment due to AD. This will be helpful for clinical trials and hopefully identify those for specific treatment.
- In addition, blood-based biomarkers can identify those with preclinical AD that can targeted for prevention/prevention trials.

Thanks to Randall Bateman and Suzanne Schindler at Washington University!